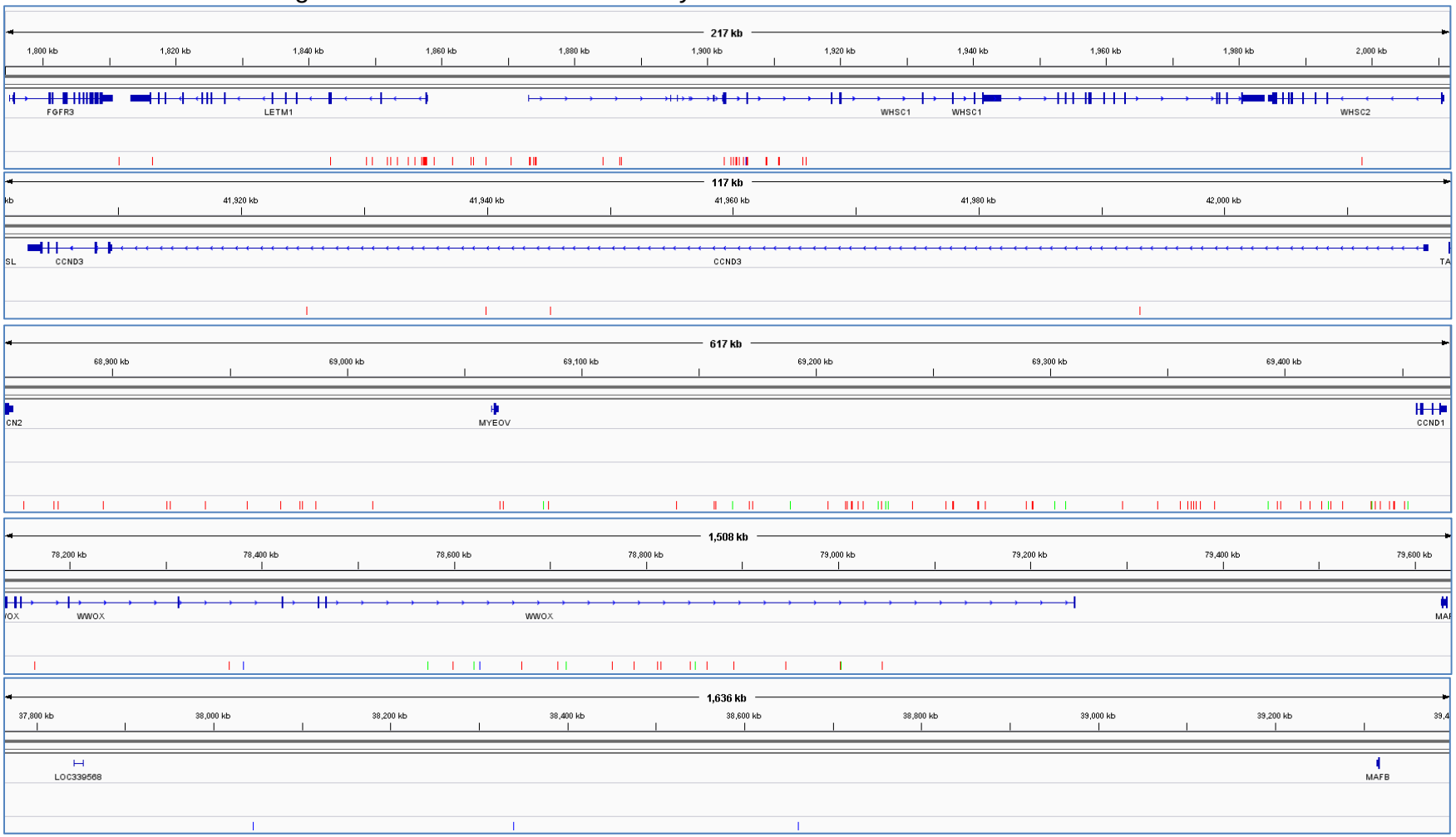
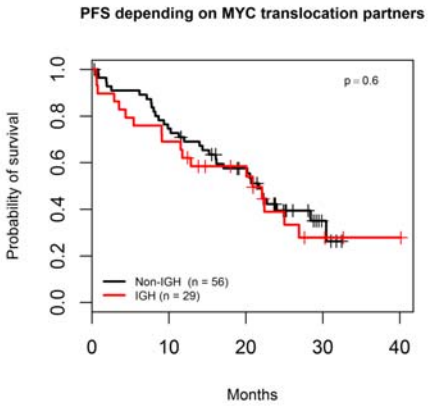
Walker et al. APOBEC signatures and translocations in myeloma

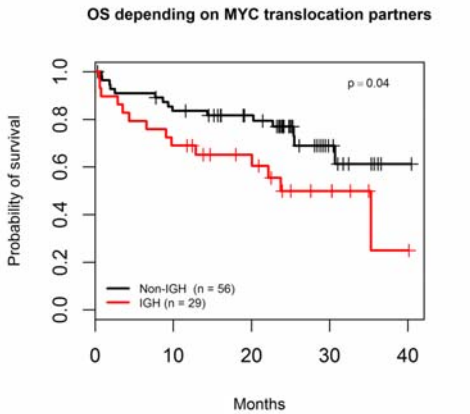


Supplementary Figure 1: Location of translocation breakpoints

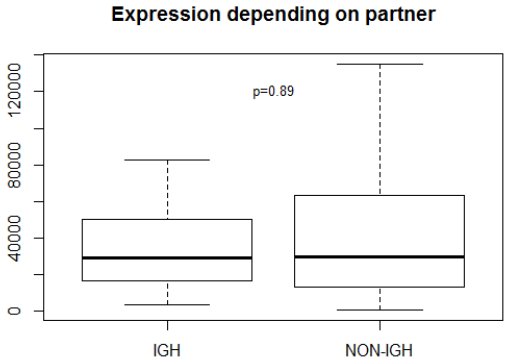
A



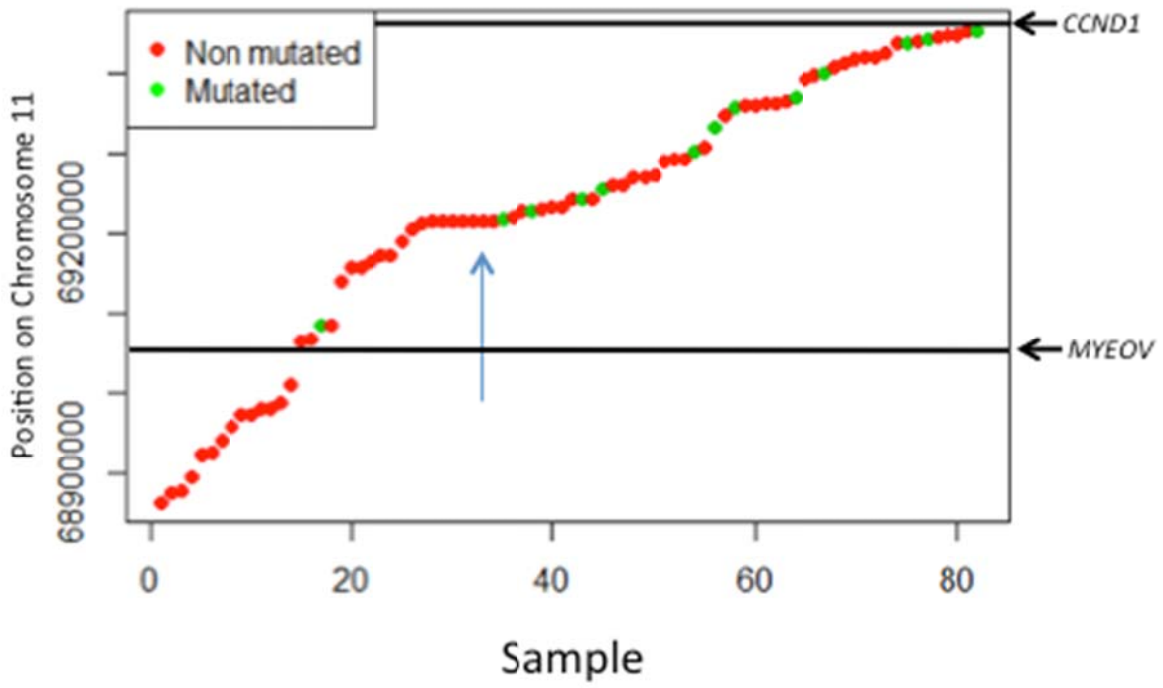
B



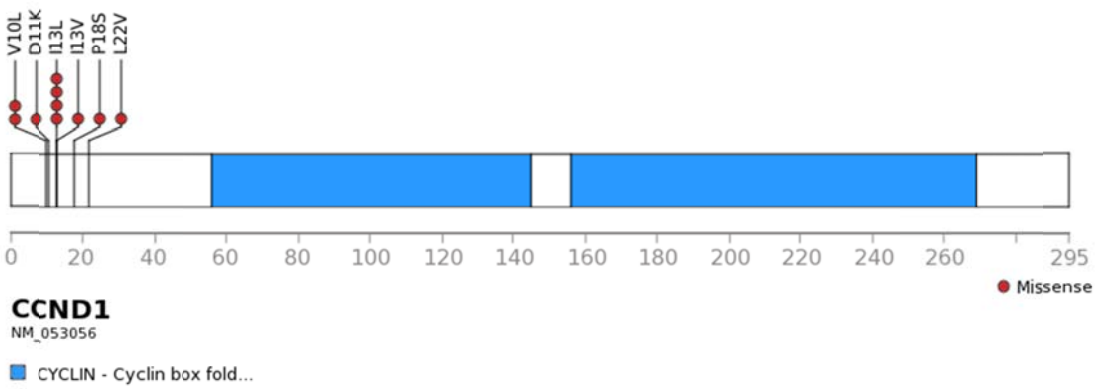
C



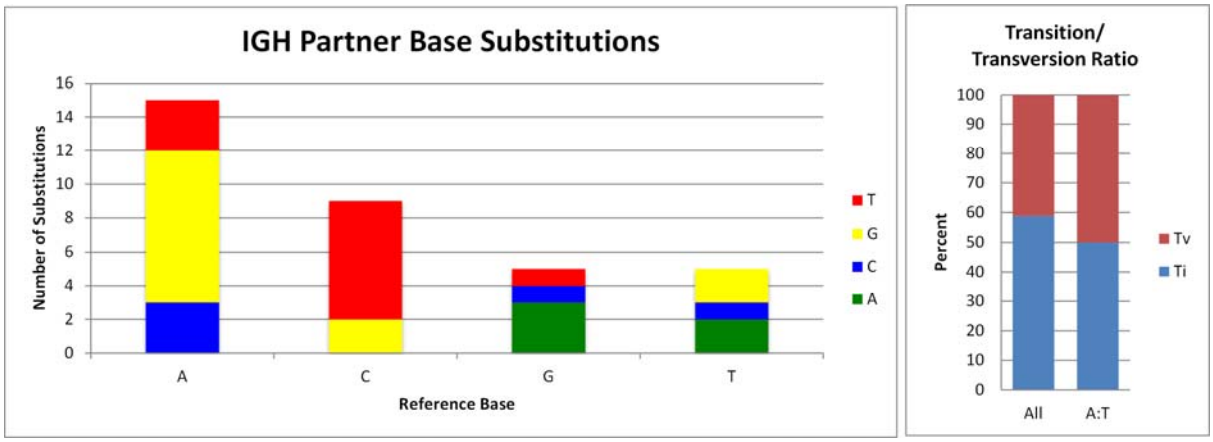
Supplementary Figure 2. *MYC* translocation partner and the effect on PFS (A), OS (B) and MYC expression (C). Box plots show minimum and maximum values in the whiskers and 25 and 75 percentiles in the box. The median value is shown by the bold line.



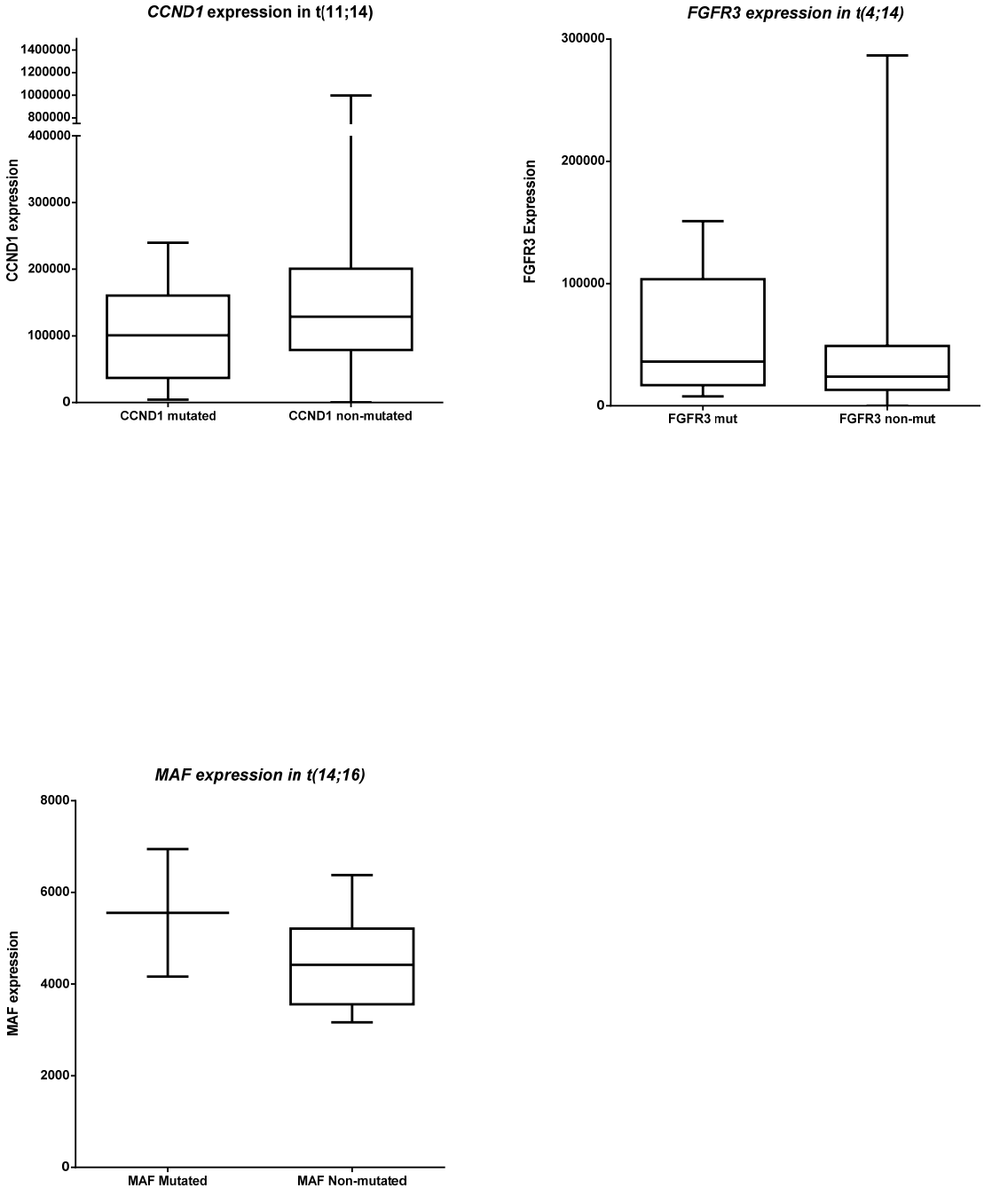
Supplementary Figure 3: t(11;14) breakpoints annotated according to *CCND1* mutation status indicates samples with a breakpoint closer to *CCND1* are more likely to have a mutated *CCND1* (p=0.03).



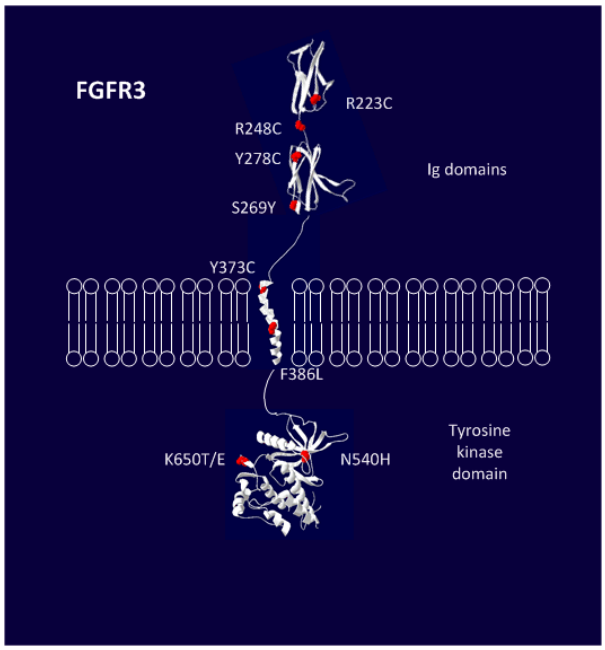
Supplementary Figure 4: CCND1 mutations in the Myeloma **I**X dataset.



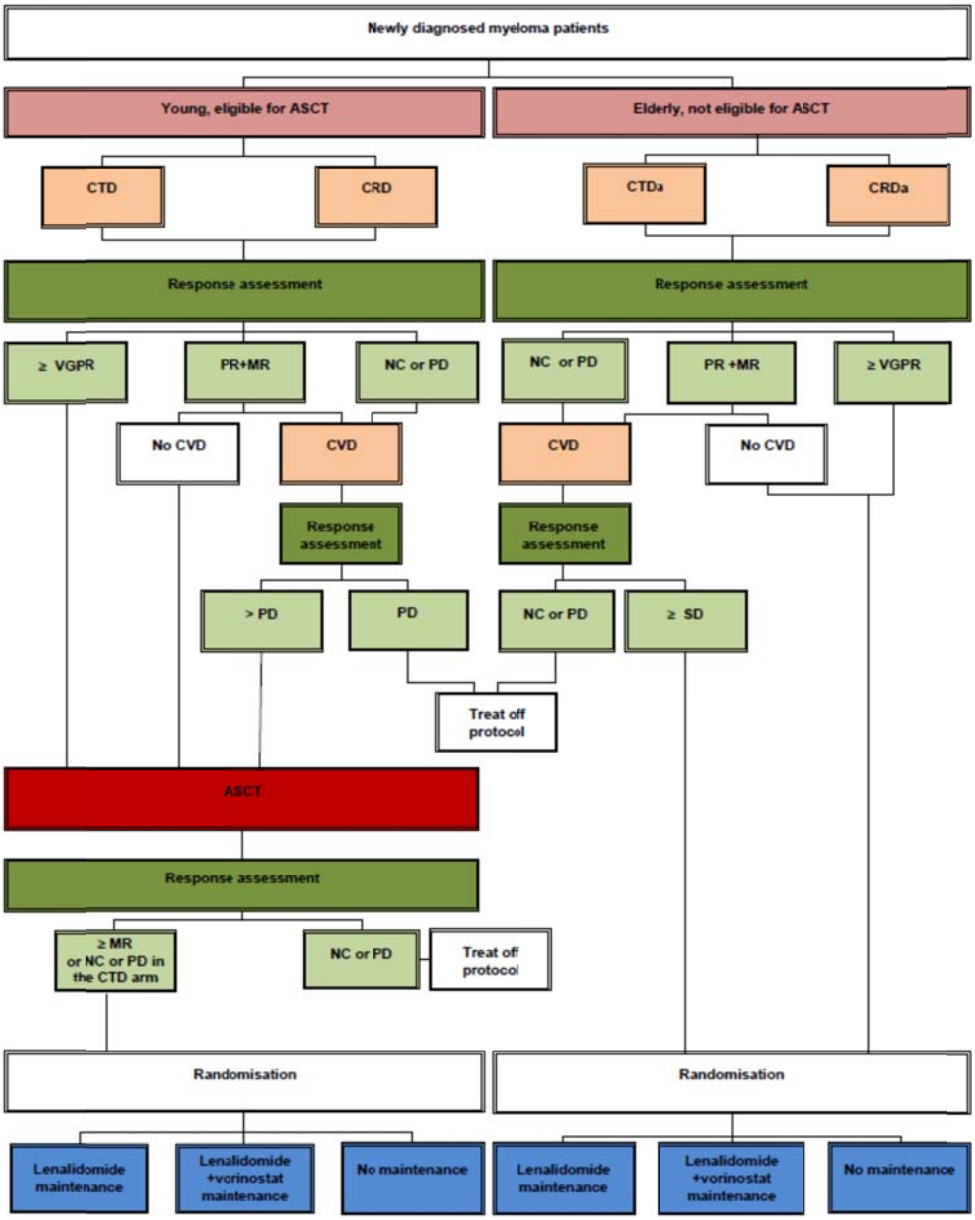
Supplementary Figure 5. The mutational pattern in translocation partner genes indicates that AID is responsible. AID is targeted to WRC motifs where the C is deaminated to U. This is repaired through replication, UNG or mismatch repair where error prone polymerases lead to transitions and transversions at surrounding A:T bases. This results in ~60% of mutations that arise through somatic hypermutation are in A:T bases and half of those are trasnversions. Here, we show the base changes in the IGH translocation partner oncogenes, where 58.8% of mutations are in A:T bases and exactly 50% of those are transversions.



Supplementary Figure 6 There is no significant expression difference between mutated and non-mutated translocation partner genes. Box plots show minimum and maximum values in the whiskers and 25 and 75 percentiles in the box. The median value is shown by the bold line.



Supplementary Figure 7: *FGFR3* mutations activate the RAS pathway in myeloma cell lines. Crystal structure of FGFR3 with mutations marked in red. The extracellular immunoglobulin (Ig) domains, transmembrane and tyrosine kinase domains were taken from protein databank IDs of 3GRW, 2LZL and 4K33, respectively.



Supplementary Figure 8. Consort Diagram of the trial design for Myeloma XI.

Supplementary Table 1: Metrics for sequencing data.

Feature	Normal 463	Tumour 463	Combined 926
Median depth	58.7 (19,179)	60.0x (28,198)	59.3x (19,198)
20x coverage %	85.7 (46.8,97.0)	86.4 (60.5,97.9)	86.0 (46.8,97.9)
Duplication %	12.0 (0.1,83.6)	10.3 (0.1,76.6)	11.2 (0.1,83.6)

Power calculation: based on 463 patients and a mutation frequency of 1.5 mutations/Mb we calculate we have 99% power to detect mutations in 5% of patients and 69% power to detect mutations in 3% of patients (based on data from Lawrence et al. 2014 *Nature* **505**:7484).

Supplementary Table 2: t(11;14) samples have a higher incidence of the G allele at rs9344.

	CHR	t11;14 GG/GA/AA	non t11;14 GG/GA/AA	dbSNP build 138	BP	A1	TEST	NMISS	SE	OR	L95	U95	STAT	P
UK GWAS	11	57/41/10	197/313/135	rs9344	69462910	A	ADD	753	0.1613	0.4857	0.3541	0.6663	-4.478	7.55E-06
German GWAS	11	76/86/17	186/360/163	rs9344	69462910	A	ADD	888	0.1274	0.5287	0.4119	0.6787	-5.003	5.68E-07
UK seq	11	45/35/6	116/181/78	rs9344	69462910	A	ADD	463	0.1874	0.4721	0.327	0.6816	-4.006	6.19E-05

	CHR	t11;14 GG/GA/AA	non t11;14 GG/GA/AA	dbSNP build 138	BP	A1	N	P	P(R)	OR	L95	U95	OR(R)	Q	I^2
Combined	11	178/162/33	499/854/376	rs9344	69462910	A	3	6.33E-15	6.33E-15	0.5027	0.42	0.59	0.5027	0.8545	0

Supplementary Table 3: Variants found in translocation partner oncogenes. SIFT predictions for translocation partner gene mutations. SIFT scores <0.05 are predicted as damaging (red), and those at 0.06 (orange) could also be considered damaging. Distances from the nearest AID WRC motif are shown from the consensus C base.

Sample	Tx	Chr	Position	Ref	Alt	Transcript change	Refseq ID	TI/TV	X_TO_Y_ SIXTYPES	CONTEXT	Variant type	Exon	Gene	Protein change	Variant classification	SIFT Score	WRC motif
12-0440-B-BMA-R138-DNA	4	4	1803398	C	T	c.667C>T	NM_000142	Ti	C>T/G>A	CxG	SNP	6	FGFR3	p.R223C	Missense_Mutation	0	-7
11-946-B-R138-DNA	4	4	1803564	C	T	c.742C>T	NM_000142	Ti	C>T/G>A	GxG	SNP	7	FGFR3	p.R248C	Missense_Mutation	0	0
12-0459-B-BMA-R138-DNA	4	4	1803564	C	T	c.742C>T	NM_000142	Ti	C>T/G>A	GxG	SNP	7	FGFR3	p.R248C	Missense_Mutation	0	0
12-1646-B-BMA-R138-DNA	4	4	1803564	C	T	c.742C>T	NM_000142	Ti	C>T/G>A	GxG	SNP	7	FGFR3	p.R248C	Missense_Mutation	0	0
11-1186-B-BMA-R138-DNA	4	4	1803627	A	C	c.805A>C	NM_000142	Tv	T>G/A>C	CxG	SNP	7	FGFR3	p.S269R	Missense_Mutation	0	-2
12-0156-B-BMA-R138-DNA	4	4	1803655	A	G	c.833A>G	NM_000142	Ti	T>C/A>G	TxC	SNP	7	FGFR3	p.Y278C	Missense_Mutation	0	-1
12-1865-B-BMA-R138-DNA	4	4	1806099	A	G	c.1118A>G	NM_000142	Ti	T>C/A>G	TxT	SNP	9	FGFR3	p.Y373C	Missense_Mutation	0.01	-3
11-715-B-R138-DNA	4	4	1806139	C	G	c.1158C>G	NM_000142	Tv	C>G/G>C	TxA	SNP	9	FGFR3	p.F386L	Missense_Mutation	0.37	+30
12-1700-B-BMA-R138-DNA	4	4	1807369	A	C	c.1618A>C	NM_000142	Tv	T>G/A>C	CxA	SNP	12	FGFR3	p.N540H	Missense_Mutation	0	-2
12-1700-B-BMA-R138-DNA	4	4	1807889	A	G	c.1948A>G	NM_000142	Ti	T>C/A>G	GxA	SNP	14	FGFR3	p.K650E	Missense_Mutation	0	+4
12-0197-B-BMA-R138-DNA	4	4	1807890	A	C	c.1949A>C	NM_000142	Tv	T>G/A>C	AxG	SNP	14	FGFR3	p.K650T	Missense_Mutation	0	+5
11-1186-B-BMA-R138-DNA	4	4	1808856	T	A	c.2288T>A	NM_000142	Tv	T>A/A>T	CxG	SNP	18	FGFR3	p.L763Q	Missense_Mutation	0	+8
11-1227-B-BMA-R138-DNA	11	11	69456087	A	T	c.6A>T	NM_053056	Tv	T>A/A>T	AxC	SNP	1	CCND1	p.E2D	Missense_Mutation	0.06	-1
11-1152-B-BMA-R138-DNA	11	11	69456116	C	T	c.35C>T	NM_053056	Ti	C>T/G>A	AxC	SNP	1	CCND1	p.T12I	Missense_Mutation	0.39	0
10-183-B-R138-DNA	11	11	69456179	A	G	c.98A>G	NM_053056	Ti	T>C/A>G	AxG	SNP	1	CCND1	p.K33R	Missense_Mutation	0.43	+4
11-315-B-R138-DNA	11	11	69456200	C	T	c.119C>T	NM_053056	Ti	C>T/G>A	CxC	SNP	1	CCND1	p.P40L	Missense_Mutation	0.05	+5
11-1152-B-BMA-R138-DNA	11	11	69456205	G	T	c.124G>T	NM_053056	Tv	C>A/G>T	GxT	SNP	1	CCND1	p.V42L	Missense_Mutation	0.4	-8
11-1227-B-BMA-R138-DNA	11	11	69456211	T	A	c.130T>A	NM_053056	Tv	T>A/A>T	CxA	SNP	1	CCND1	p.Y44N	Missense_Mutation	0	-2
12-1525-B-BMA-R138-DNA	11	11	69456211	T	G	c.130T>G	NM_053056	Tv	T>G/A>C	CxA	SNP	1	CCND1	p.Y44D	Missense_Mutation	0	-2
11-1152-B-BMA-R138-DNA	11	11	69456215	T	G	c.134T>G	NM_053056	Tv	T>G/A>C	TxC	SNP	1	CCND1	p.F45C	Missense_Mutation	0	+2
11-017-B-R138-DNA	11	11	69456219	A	T	c.138A>T	NM_053056	Tv	T>A/A>T	AxT	SNP	1	CCND1	p.K46N	Missense_Mutation	0.03	+6
12-0994-B-BMA-R138-DNA	11	11	69456219	A	T	c.138A>T	NM_053056	Tv	T>A/A>T	AxT	SNP	1	CCND1	p.K46N	Missense_Mutation	0.03	+6
10-365-B-R138-DNA	11	11	69456221	G	C	c.140G>C	NM_053056	Tv	C>G/G>C	TxT	SNP	1	CCND1	p.C47S	Missense_Mutation	0.04	-5
11-017-B-R138-DNA	11	11	69456223	G	A	c.142G>A	NM_053056	Ti	C>T/G>A	TxT	SNP	1	CCND1	p.V48M	Missense_Mutation	0	-3
10-365-B-R138-DNA	11	11	69456230	A	G	c.149A>G	NM_053056	Ti	T>C/A>G	AxG	SNP	1	CCND1	p.K50R	Missense_Mutation	0.47	+4
12-0484-B-BMA-R138-DNA	11	11	69456230	A	G	c.149A>G	NM_053056	Ti	T>C/A>G	AxG	SNP	1	CCND1	p.K50R	Missense_Mutation	0.47	+4
12-1405-B-BMA-R138-DNA	11	11	69456230	A	G	c.149A>G	NM_053056	Ti	T>C/A>G	AxG	SNP	1	CCND1	p.K50R	Missense_Mutation	0.47	+4
12-1405-B-BMA-R138-DNA	11	11	69456256	A	G	c.175A>G	NM_053056	Ti	T>C/A>G	GxT	SNP	1	CCND1	p.I59V	Missense_Mutation	0.15	-2
11-062-B-R138-DNA	16	16	79632874	C	G	c.926G>C	NM_001031804	Tv	C>G/G>C	CxT	SNP	1	MAF	p.R309T	Missense_Mutation	0.02	+4
12-0349-B-BMA-R138-DNA	16	16	79632931	T	C	c.869A>G	NM_001031804	Ti	T>C/A>G	CxT	SNP	1	MAF	p.K290R	Missense_Mutation	0.02	+1
11-1144-B-R138-DNA	16	16	79632965	G	A	c.835C>T	NM_001031804	Ti	C>T/G>A	CxC	SNP	1	MAF	p.R279C	Missense_Mutation	0	-4
11-918-B-R138-DNA	16	16	79632973	C	T	c.827G>A	NM_001031804	Ti	C>T/G>A	CxG	SNP	1	MAF	p.R276Q	Missense_Mutation	0.06	+1
11-1144-B-R138-DNA	16	16	79632974	G	A	c.826C>T	NM_001031804	Ti	C>T/G>A	CxG	SNP	1	MAF	p.R276W	Missense_Mutation	0	-7
11-099-B-R138-DNA	20	20	39316611	A	G	c.880T>C	NM_005461	Ti	T>C/A>G	TxG	SNP	1	MAFB	p.Y294H	Missense_Mutation	0.03	-6
10-141-B-R138-DNA	-	4	1957576	GGTGTGAG	G	c.2675_splic	NM_001042424	-	-	-	DEL	14	WHSC1	p.R892_s	Splice_Site	0	+2
10-141-B-R138-DNA	-	4	1932437	A	C	c.1495A>C	NM_001042424	Tv	T>G/A>C	GxG	SNP	6	WHSC1	p.R499R	Silent	1	+3
10-141-B-R138-DNA	-	4	1952861	A	G	c.1944A>G	NM_001042424	Ti	T>C/A>G	AxA	SNP	10	WHSC1	p.Q648Q	Silent	1	-2
10-141-B-R138-DNA	-	4	1978255	G	A	c.3675G>A	NM_001042424	Ti	C>T/G>A	CxA	SNP	21	WHSC1	p.T1225T	Silent	1	+1
10-141-B-R138-DNA	-	4	1920027	G	A	c.1087G>A	NM_001042424	Ti	C>T/G>A	GxC	SNP	5	WHSC1	p.A363T	Missense_Mutation	0.57	-10
11-987-B-R138-DNA	-	4	1955131	C	T	c.2218C>T	NM_001042424	Ti	C>T/G>A	CxA	SNP	12	WHSC1	p.H740Y	Missense_Mutation	0	+1